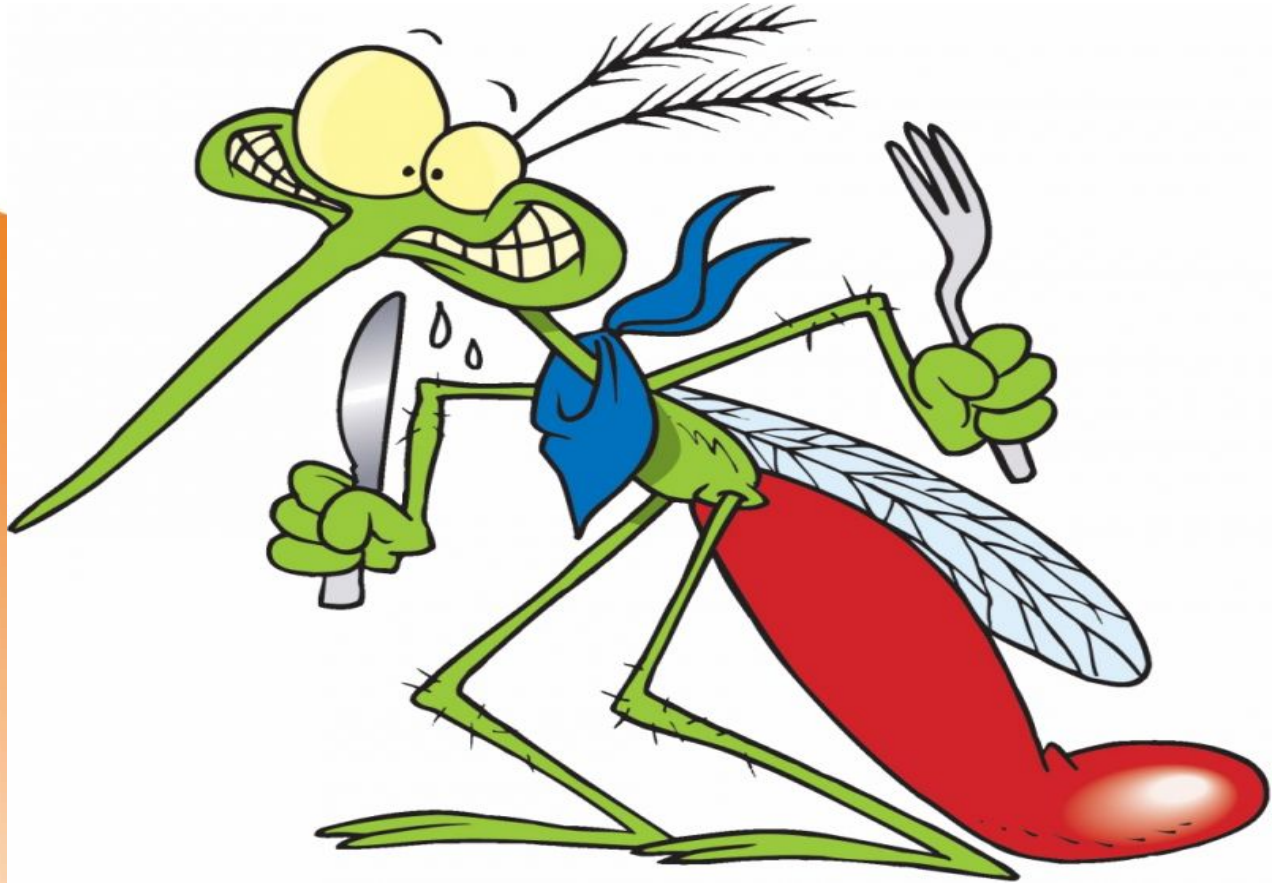
Malaria
“Bad Air”



Malaria: Lecture Goals

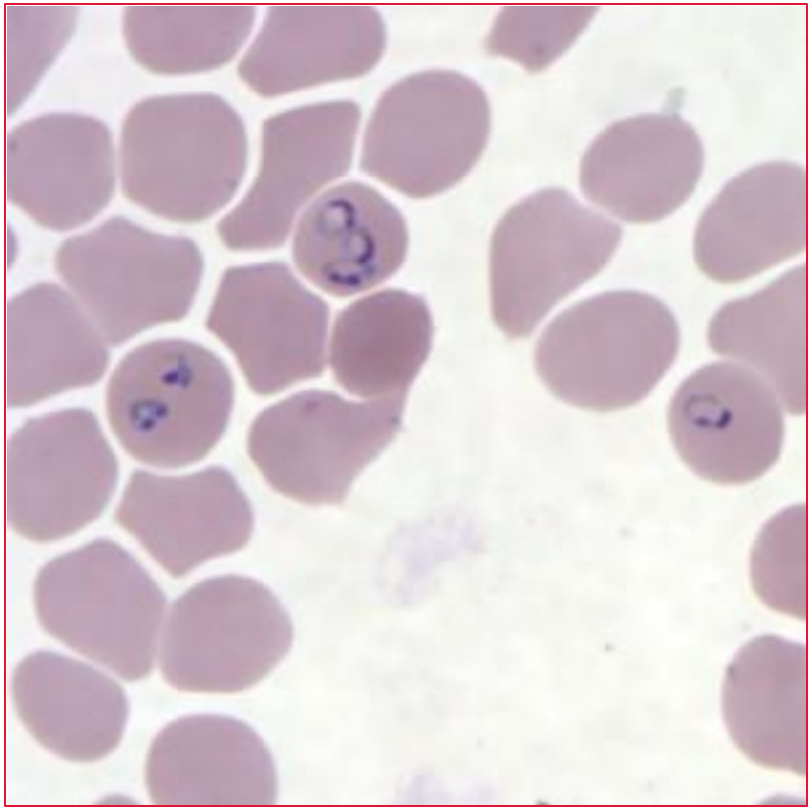
- Understand basic principles of malaria pathogenesis in the context of relevance to clinical disease and epidemiology
- Understand the clinical symptoms of malaria
- Understand the difference between uncomplicated and severe malaria
- Understand how to choose an antimalarial
- Understand where to find up-to-date resources for malaria

Outline

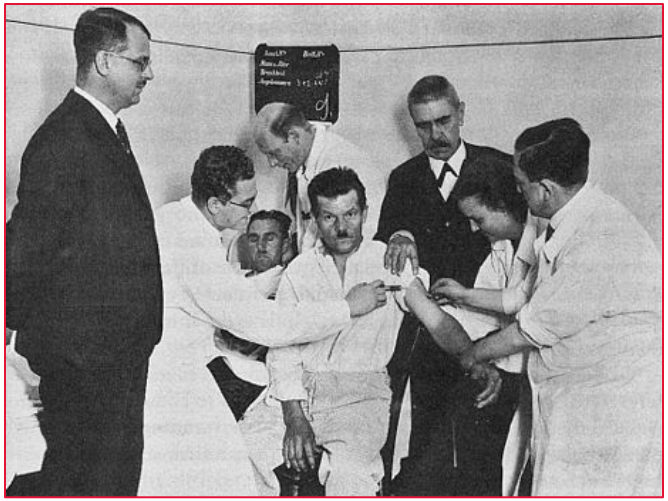
- Background
  - Organism
  - Epidemiology
  - Pathophysiology
- Clinical
  - Symptoms
  - Differential diagnosis
- Malaria in a complex emergency
  - Who is at risk
  - How to choose a medication

Malaria

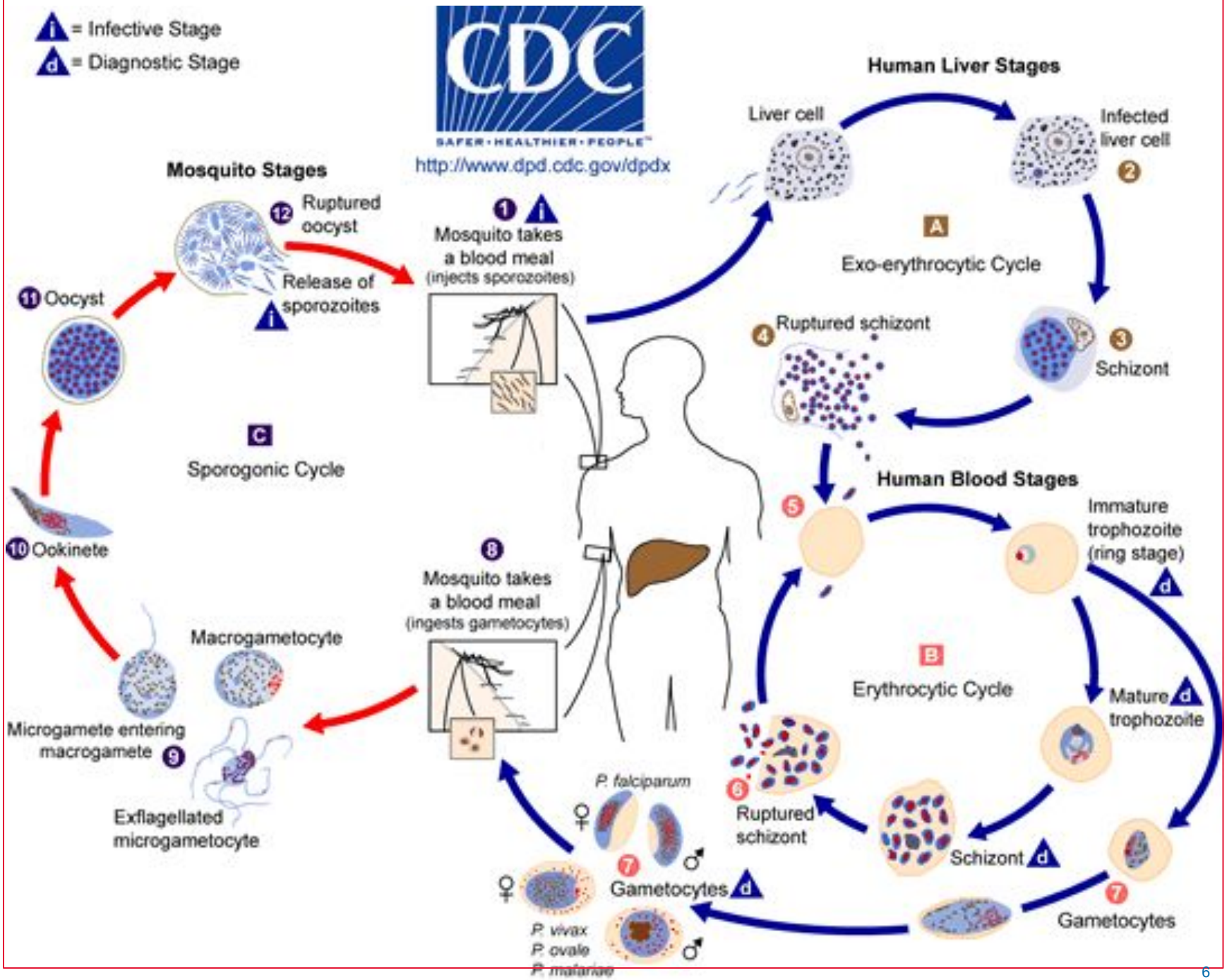
- Caused by a protozoal blood parasite
  - *Plasmodium vivax*
  - *Plasmodium ovale*
  - *Plasmodium malaria*

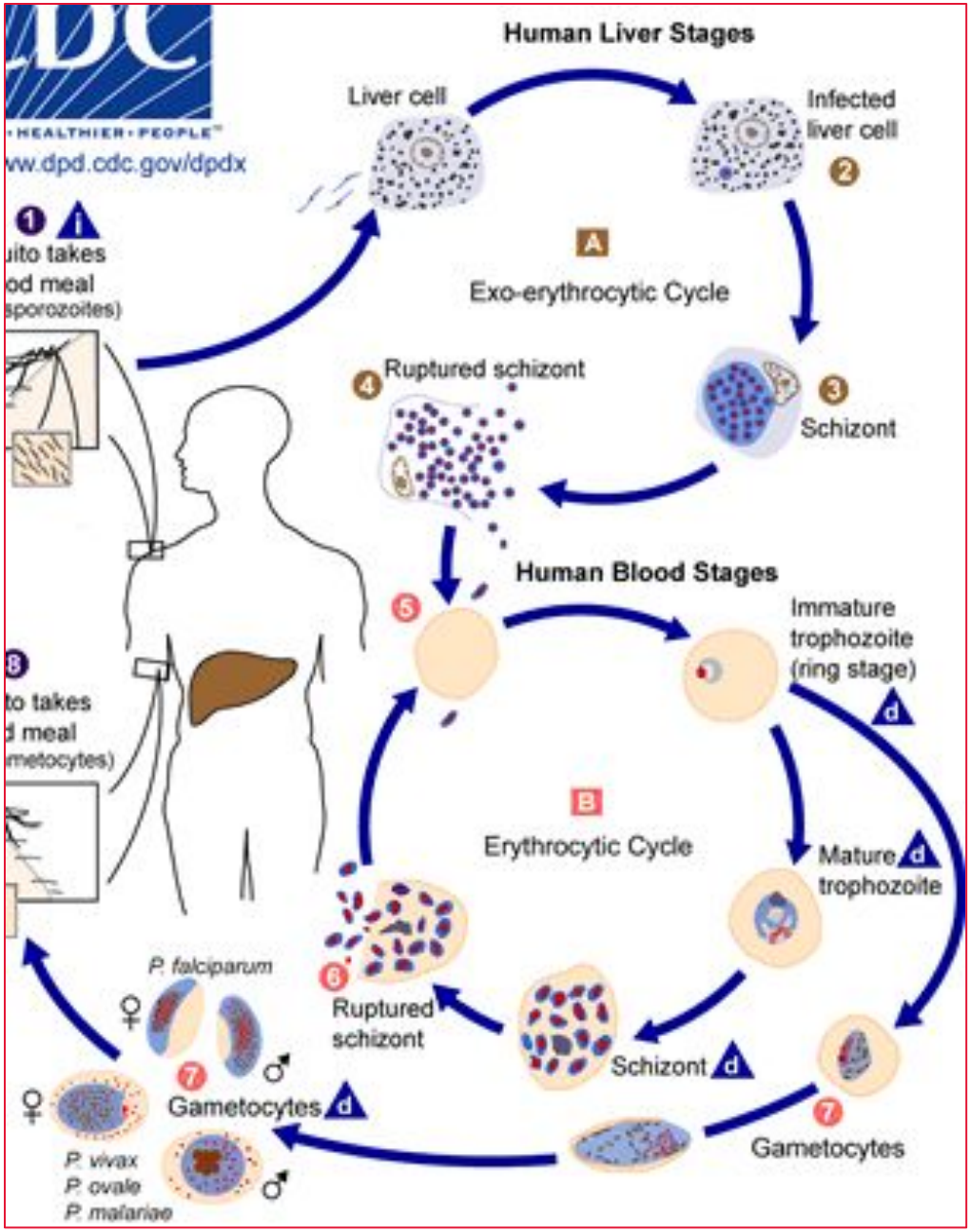


- *Plasmodium falciparum*
- *Plasmodium knowlesi*
  - *Often cause severe malaria



- Transmission: *Anopheles* mosquito
- Wide spectrum symptoms
  - Fever
  - 1927 Nobel Prize: pyrotherapy for syphilis
- Geographical distribution:
  - Tropic / Subtropics
- 350-500 million infections worldwide/year

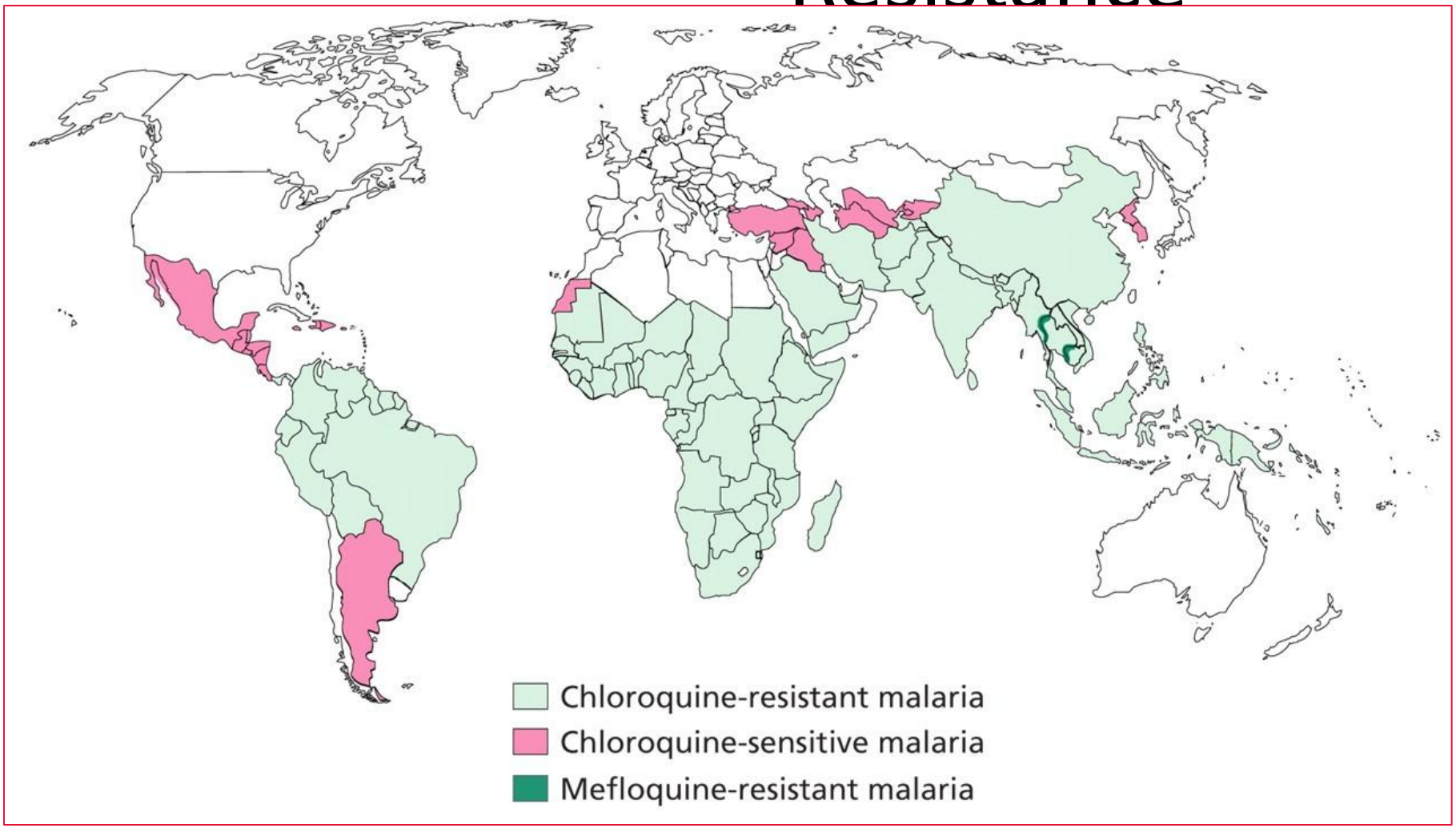

i = Infective Stage
d = Diagnostic Stage
CDC
SAFER · HEALTHIER · PEOPLE™
http://www.dpd.cdc.gov/dpdx
Human Liver Stages
Liver cell
Infected liver cell
2
A
Exo-erythrocytic Cycle
3
Schizont
4
Ruptured schizont
Human Blood Stages
5
Immature trophozoite (ring stage)
d
Mature trophozoite
d
B
Erythrocytic Cycle
6
Ruptured schizont
Schizont
d
7
Gametocytes
Gametocytes
d
P. falciparum
P. vivax
P. ovale
P. malariae
8
Mosquito takes a blood meal
(ingests gametocytes)
Macrogametocyte
Microgamete entering macrogamete
9
Exflagellated microgametocyte
10
Ookinete
11
Oocyst
12
Ruptured oocyst
Release of sporozoites
Mosquito Stages
1
Mosquito takes a blood meal
(injects sporozoites)
C
Sporogonic Cycle



- **Liver stage:** Asimptomatic. With *P. vivax* and *P. ovale*, has dormant form (hypnozoite) that can relapse much later. This form is not killed by most malaria medications.

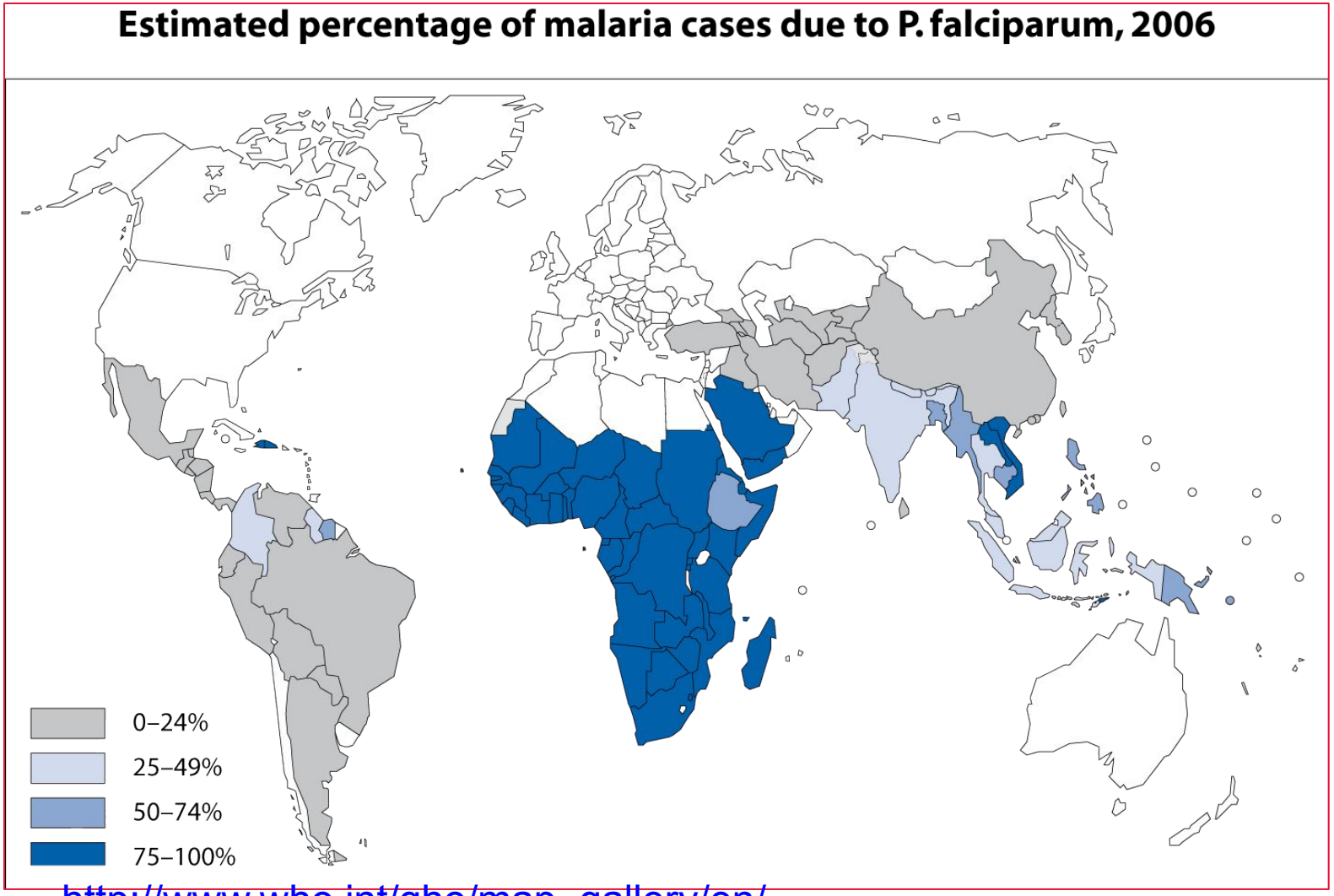
- **Blood stage:** Symptomatic. Notice the continuous circle. This will continue until medication or immune system eradicates (1-5+ years untreated). Once cycle 3-4 days, except *P. falciparum*.

Malaria: Endemicity and Resistance



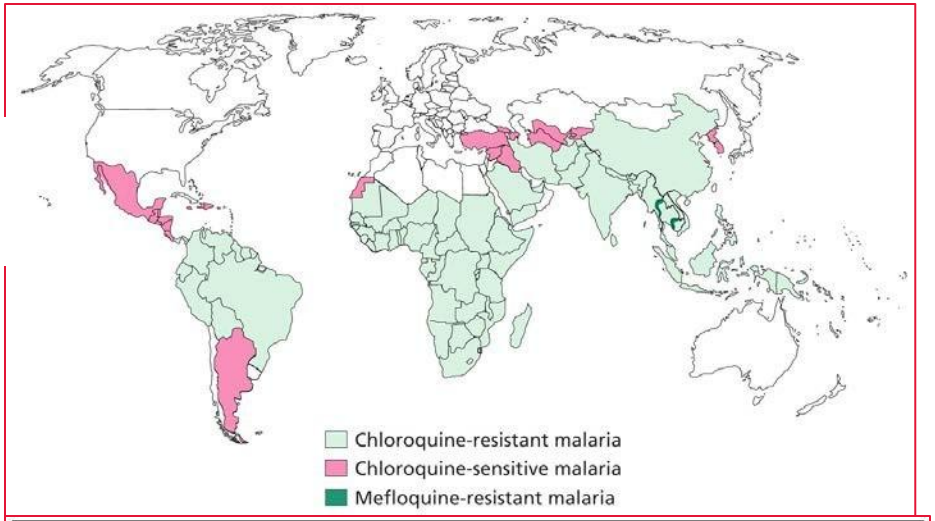
POWELL B , FORD C Cleveland Clinic Journal of Medicine 2010;77:246-254

% Malaria *P. falciparum*



http://www.who.int/gho/map_gallery/en/

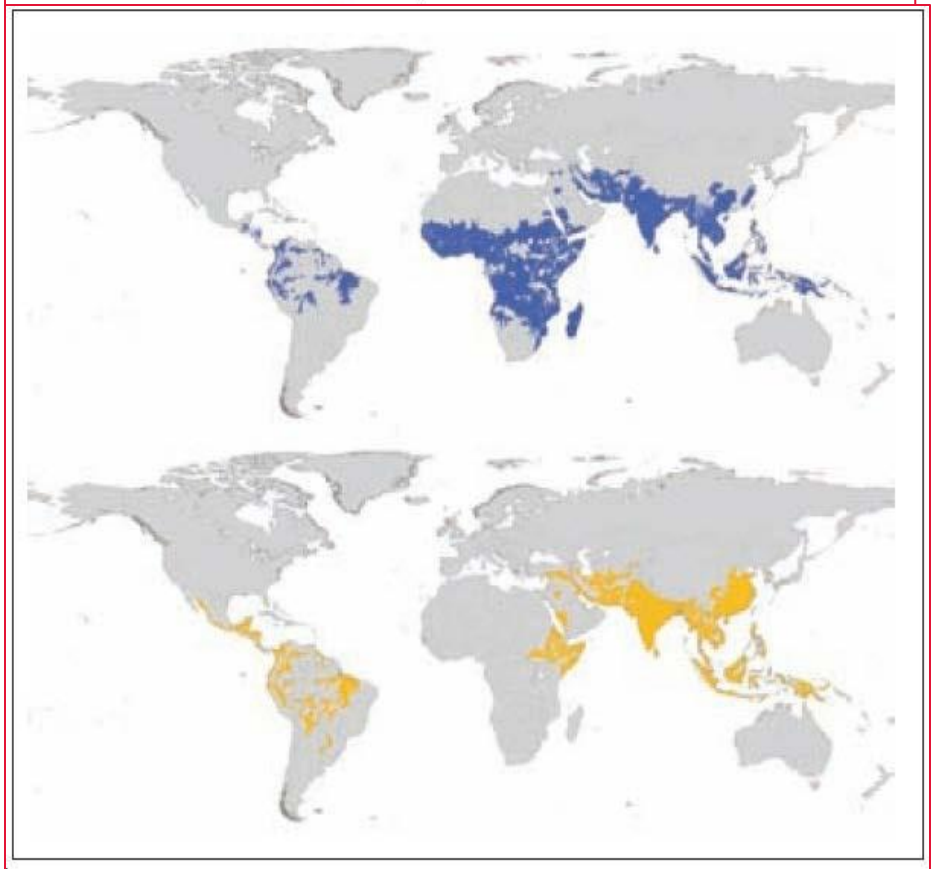
Chloroquine Resistance



- Chloroquine resistance and *P. falciparum* overlap, with exceptions:
  - Central America West of Panama Canal
  - Haiti/Dominican Republic
  - Middle East
  - **Make easy: Rx *P. falciparum* with ACT**

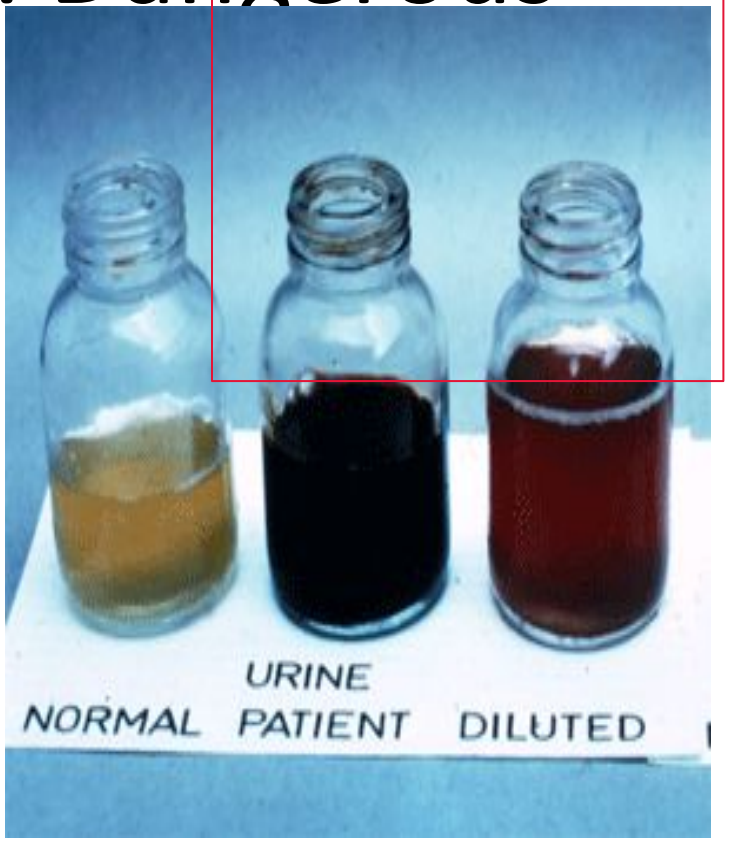
***P. falciparum* areas**

***P. vivax* areas**



- Mixed infection possible
  - **Asia 20-30%**
  - Africa usually *P. falciparum*
  - Americas usually *P. vivax*

P. falciparum: Dangerous



- Infects various RBC stages
- Makes RBCs "sticky"
- Result:
  - Severe hemolysis
  - Obstruction of microcirculation
  - Obstruction of capillaries
- Holo/hyperendemic
- Good News? Does not have hypnozoite
  - Hypnozoite: dormant liver form that causes relapse with *P. ovale*, *P. vivax*

Malaria in a Complex Emergency: Symptoms

- **SEVERE**
- **> 5% parasitemia**
- Severe anemia
- Hemoglobinuria
- Bleeding diathesis
- Shock/Hypotension
- Renal failure
- Hypoglycemia
- Acidosis

- UNCOMPLICATED
- Fever
  - Not always cyclic!
- Chills, sweats
- Headache
- Myalgia
- Diarrhea, nausea, emesis
- Anemia (pallor of palms)
- Thrombocytopenia

Malaria in a Complex Emergency: Who is at Risk for severe disease?

- Highest risk populations:
  - Non-immune
  - Immunocompromised, malnourished
  - Infants, young children, pregnant
  - Infected with *P. falciparum*
- In endemic areas, older children and adults develop partial immunity
  - Can have “asymptomatic” infection
  - Can have subacute or chronic symptoms

Malaria in a Complex Emergency

- Displaced people within malaria endemic areas creates risk for a severe epidemic, particularly if the displaced persons are from less endemic areas (highlands to lowlands)
- Laboratory diagnosis may be impractical
- May become necessary to:
  - Treat some people based on clinical history
  - Do mass fever treatment

Malaria: Practical Aspects of Diagnosis

- Presumptive treatment has been commonplace for decades
  - Problematic, but hard to change
- Even in holoendemic countries, WHO estimates <1/3rd of febrile episodes due to malaria
- In Africa, <20% of suspected cases receive a confirmatory diagnostic test

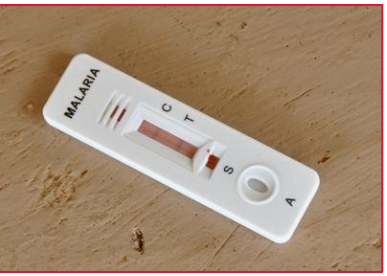
Malaria in a Complex Emergency

- Important, when possible, to at least establish a fever epidemic is due to malaria
  - Do some diagnostics
    - Combination of smears and rapid diagnostic tests
    - To establish malaria as cause
    - To monitor epidemic curve
  - Evaluate for other diseases
  - Monitor clinical response

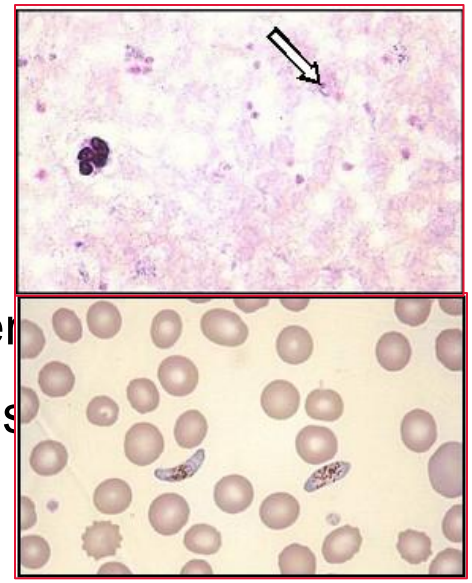
Malaria: Differential Diagnosis

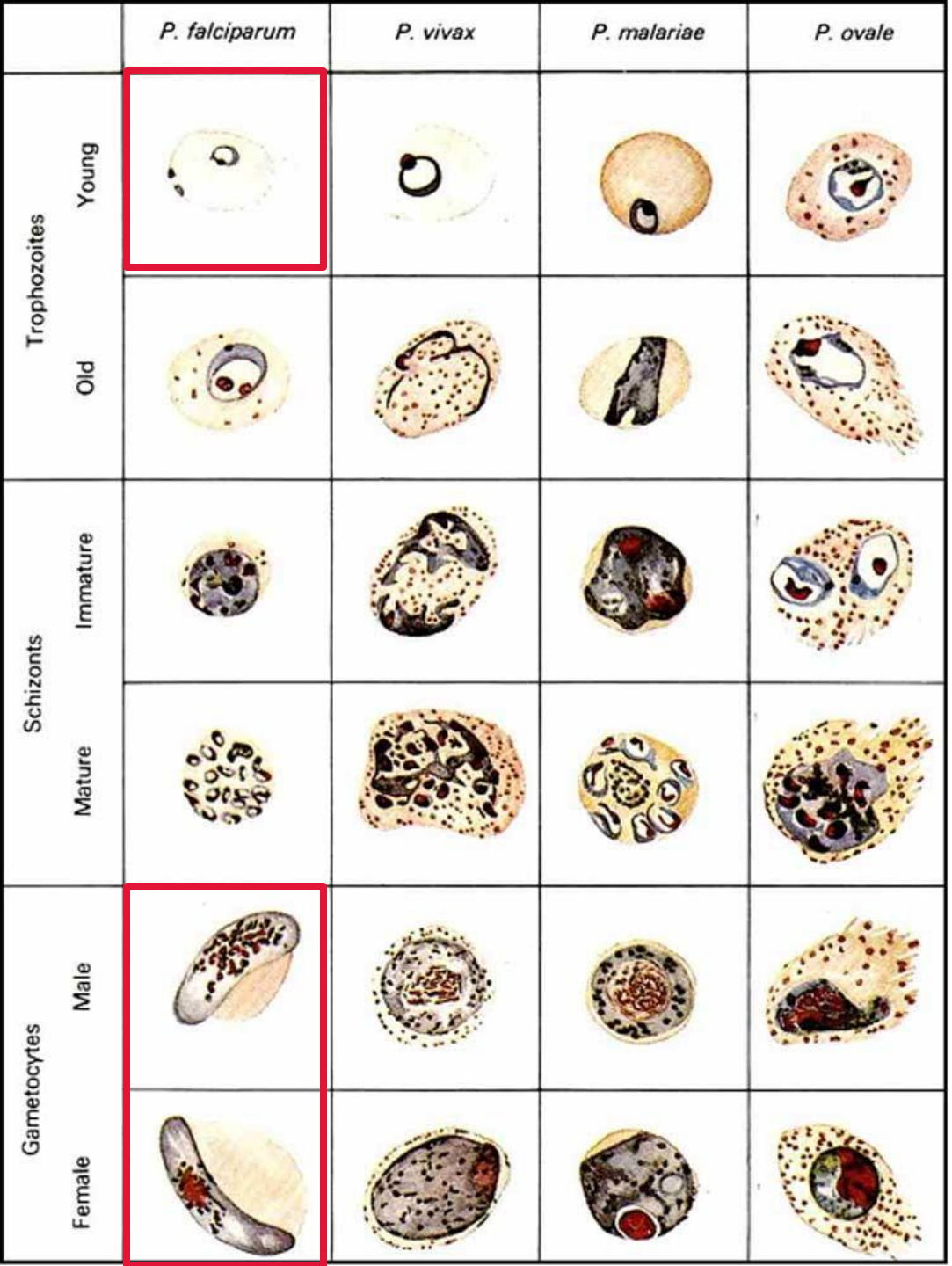
- Malaria can involve many organs
- Coinfection well described
- Differential diagnosis is broad
  - *Salmonella typhi* and non-typhi
  - *Staphylococcus aureus* with focus (bone, joint, muscle, lung, heart)
  - Dengue, yellow fever, japanese encephalitis
  - Pneumonia
  - Viral and bacterial meningitis/encephalitis
  - Leshmaniasis
  - Schistosomiasis
  - Tuberculosis
  - Liver abscess/cholangitis
  - Oncologic process

Malaria: Diagnostics



- Rapid diagnostic test (RDT)
  - Lateral flow test, relies on antibody-antigen interactions
    - Some RDTs specific for *P. falciparum*
    - WHO quality assurance programs underway
- Clinician/Public acceptance large problem
  - USA: only to confirm species
- Microscopy
  - Thick: diagnosis
  - Thin
- Identification and parasiter
- % parasitized RBCs

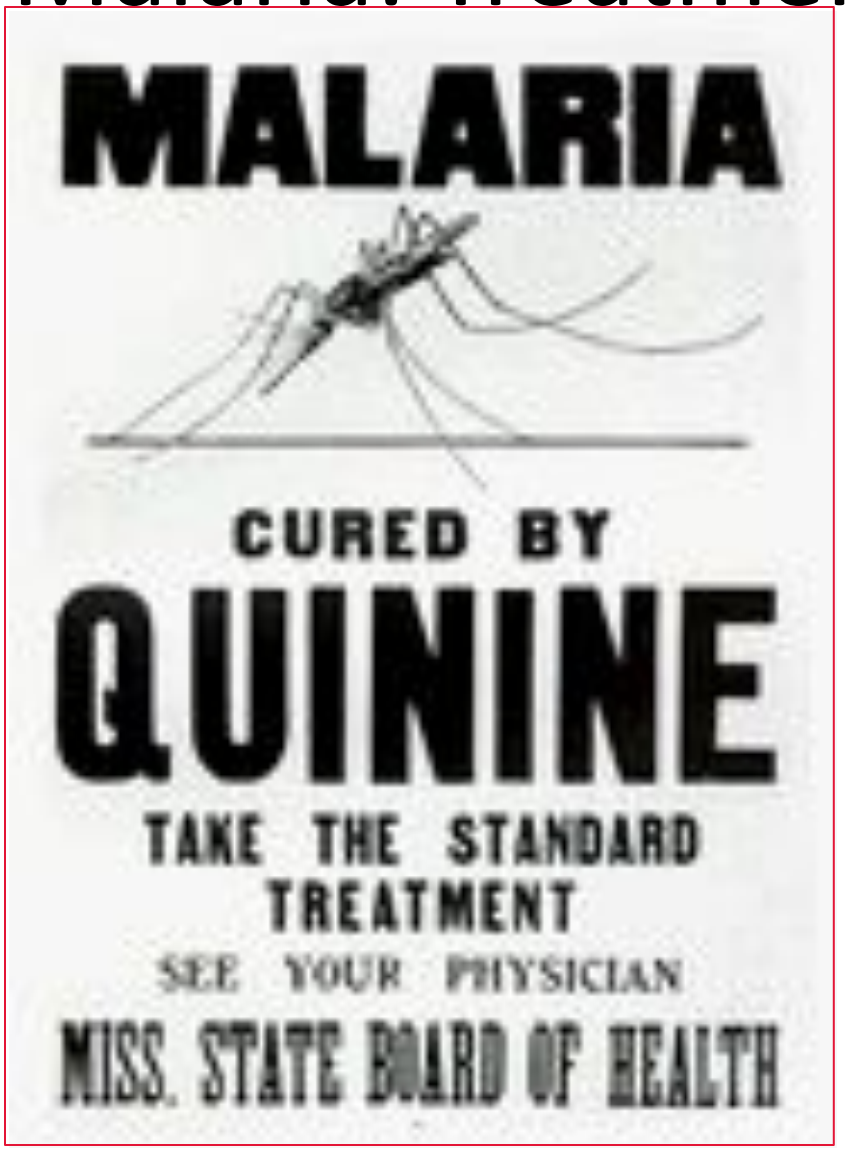


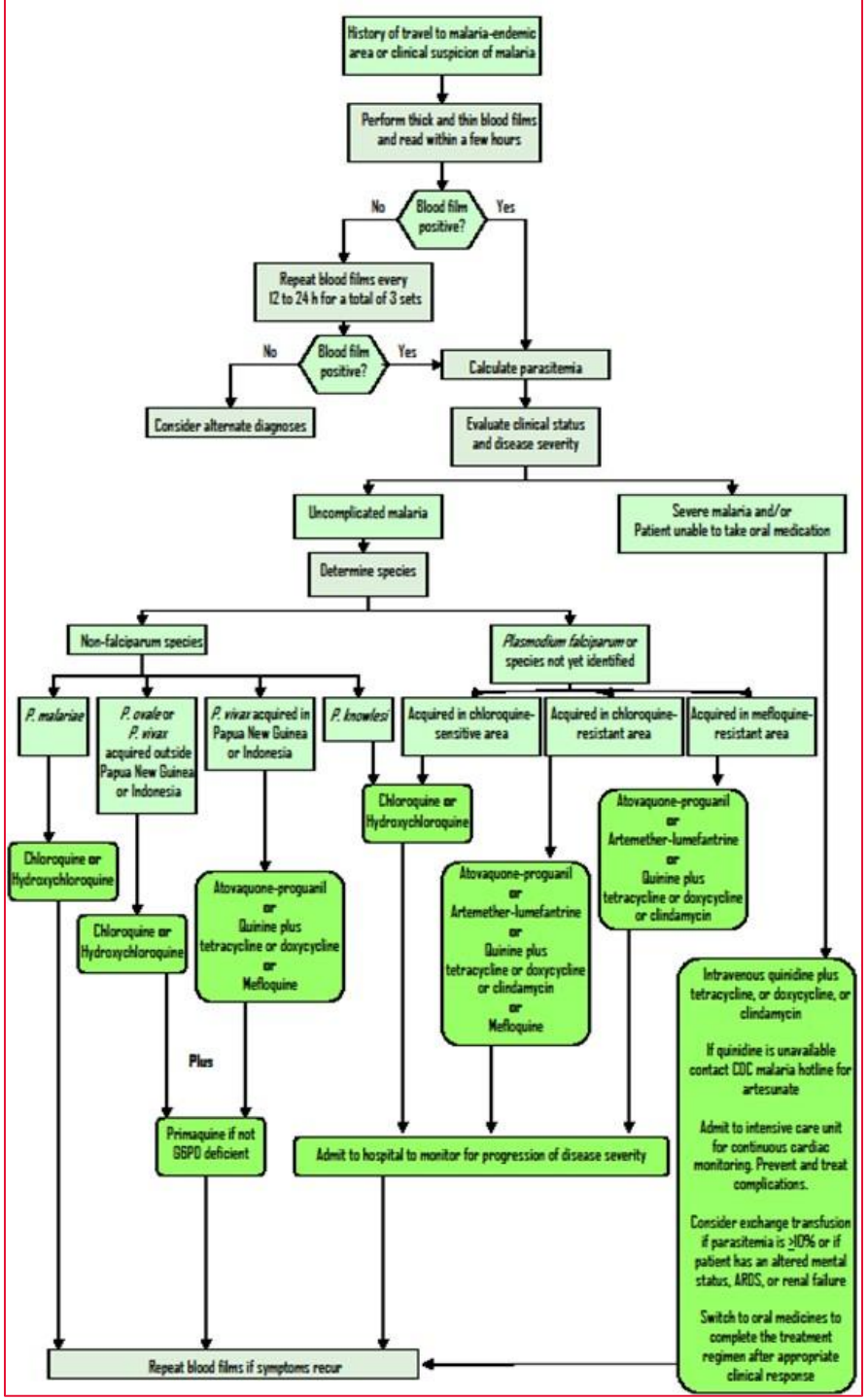


Clues to *P. falciparum*:

- Trophozoites most commonly seen, and are small, delicate rings, often multiple per RBC; infect all ages of RBC. Gametocytes "banana" shaped.

Malaria: Treatment



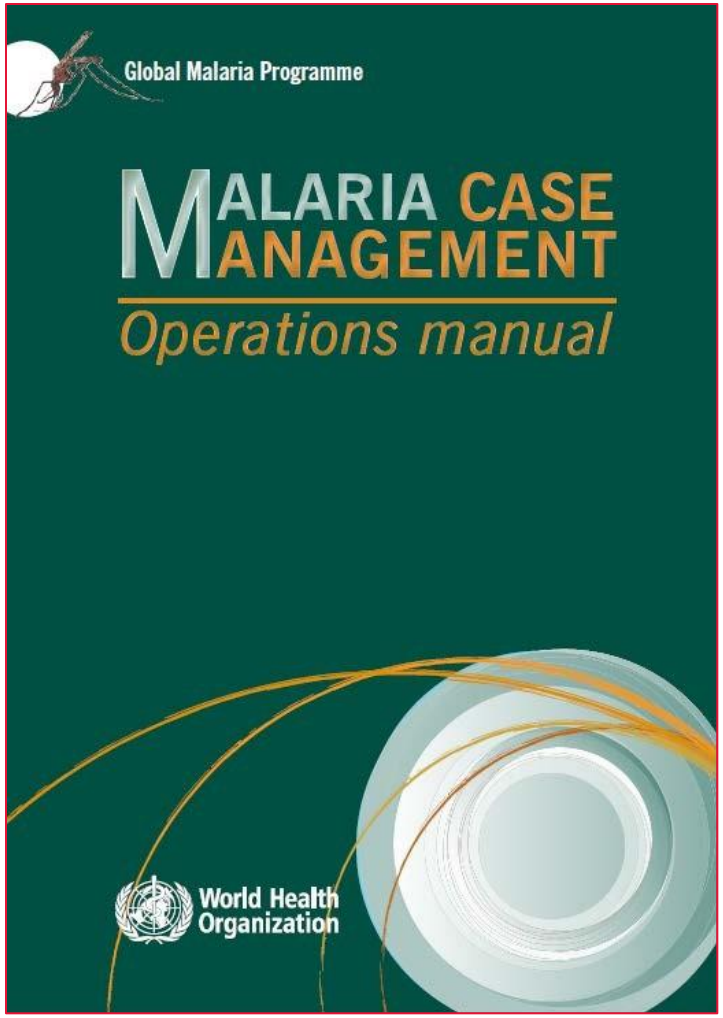


CDC Algorithm for Traveler Returned to US

***Not the same as WHO**

Note: CDC now recommending treating severe malaria with artesunate; treat with atovoquone-proquanil until it arrives (5-12 hours). To enroll a patient with severe malaria in this treatment protocol, contact the CDC Malaria Hotline: 770-488-7788 (M-F, 8am-4:30pm, eastern time) or after hours, call 770-488-7100 and request to speak with a CDC Malaria Branch clinician.
http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html

Malaria: Treatment

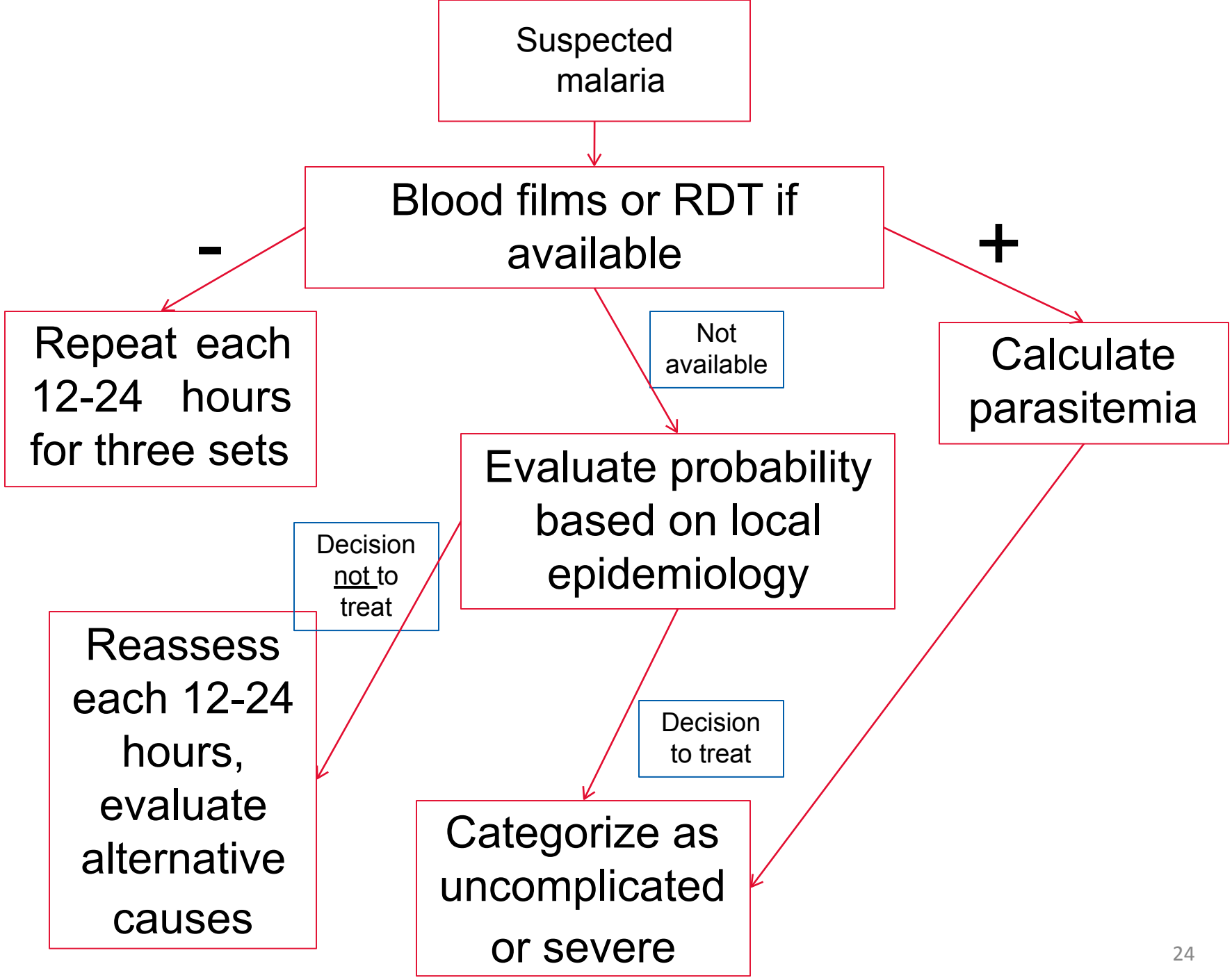


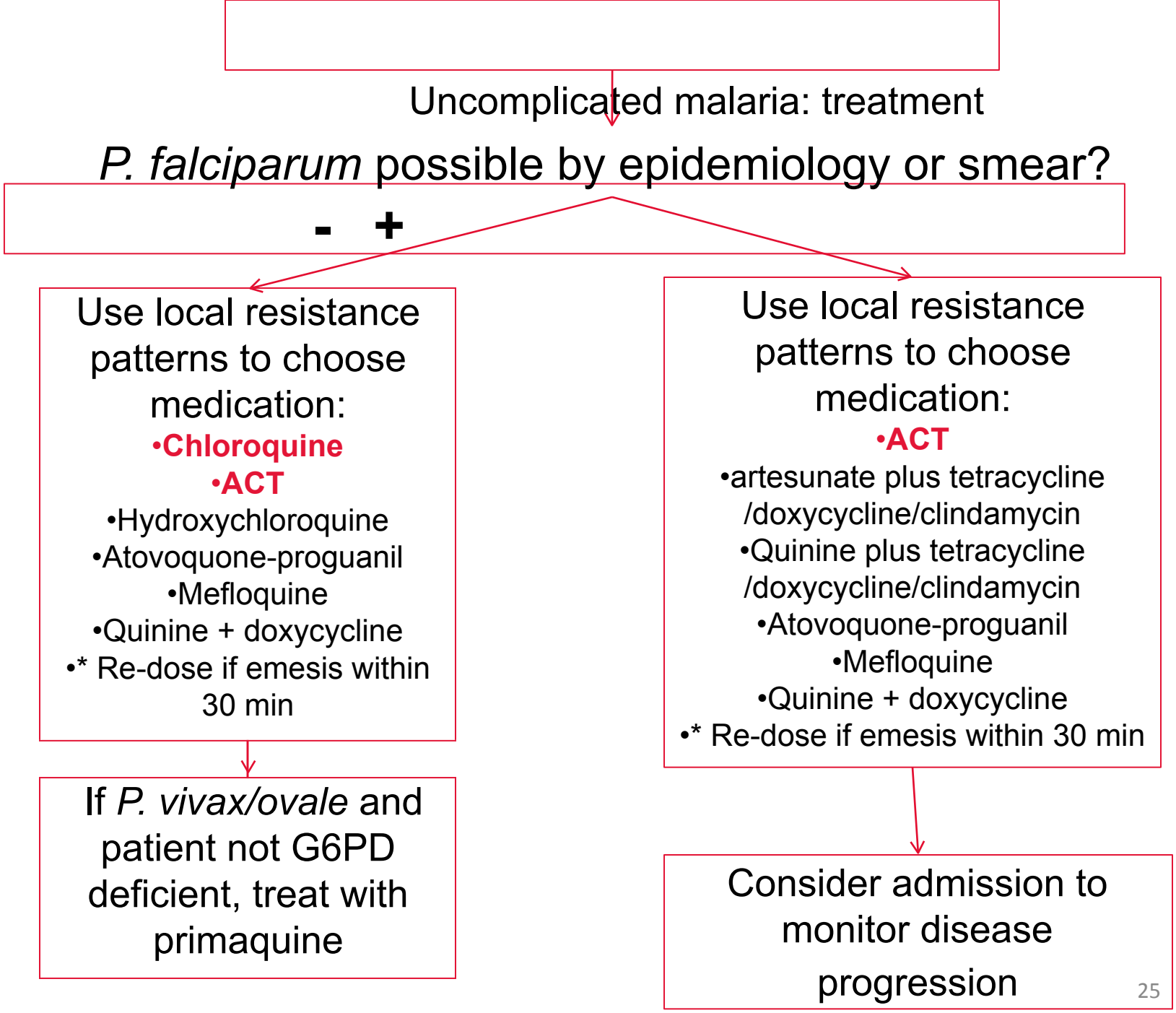
WHO guidelines and update can be found at: http://www.who.int/malaria/publications/atoz/9789241549127/en/

Malaria: Therapy Options

Default ACT in the Interagency Emergency Health Kit

- ACT (Artemisinin based combination therapies)
  - **Artemethur + lemefantrine (coartem®)**
  - Artesunate + amodiaquine (coarsucam/ASAQ Winthrop®)
  - Artesunate + mefloquine (AS+MQ)
  - Artesunate + sulfadoxine-pyrimethamine (AS+SP)
    - Not for *P. vivax*
- Artesunate + doxycycline or clindamycin
- Dihydroartemisinin plus piperaquine (DHA+PPQ)
- Quinine + doxycyline or clindamycin
- Atovaquone + proguanil (malarone®)
- Mefloquine (larium®)
- Chloroquine (widespread resistance)
- Primaquine (kills liver phase for P. *vivax/ovale*)
- IV and IM: Artesunate, artemethur, quinine


Suspected malaria
Blood films or RDT if available
-
+
Repeat each 12-24 hours for three sets
Not available
Calculate parasitemia
Evaluate probability based on local epidemiology
Decision not to treat
Reassess each 12-24 hours, evaluate alternative causes
Decision to treat
Categorize as uncomplicated or severe


Uncomplicated malaria: treatment
P. falciparum possible by epidemiology or smear?
- +
Use local resistance patterns to choose medication:
•Chloroquine
•ACT
•Hydroxychloroquine
•Atovoquone-proguanil
•Mefloquine
•Quinine + doxycycline
•* Re-dose if emesis within 30 min
If P. vivax/ovale and patient not G6PD deficient, treat with primaquine
Use local resistance patterns to choose medication:
•ACT
•artesunate plus tetracycline /doxycycline/clindamycin
•Quinine plus tetracycline /doxycycline/clindamycin
•Atovoquone-proguanil
•Mefloquine
•Quinine + doxycycline
•* Re-dose if emesis within 30 min
Consider admission to monitor disease progression

Severe Malaria: WHO Criteria

One or more of the following:

- *Clinical features:*
- Impaired consciousness, prostration
- Failure to feed
- Seizures
- Respiratory distress
- Circulatory collapse
- Clinical jaundice plus evidence of other vital organ dysfunction
- Gross hemoglobinuria
- Abnormal spontaneous bleeding (radiological)
- Pulmonary edema

- *Laboratory findings:*
- Hypoglycemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
- Metabolic acidosis (plasma bicarbonate < 15 mmol/l)
- Severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%)
- Hemoglobinuria
- Hyperparasitaemia (> 2%/100 000/µl in low intensity transmission areas or > 5% or 250 000/µl in areas of high stable malaria transmission intensity)
- Hyperlactatemia (lactate > 5 mmol/l)
- Renal impairment (serum creatinine > 265 µmol/l)

Severe malaria: Treatment the same regardless of species!
Therapy + supportive care:

Intravenous medications available?

no

Give oral or rectal until patient can be transferred to referral center:

- rectal artesunate • quinine IM • artesunate IM • artemether IM

yes

Treat IV x 24 hours minimum
Artesunate IV or IM
Artemethur Quinine

Ongoing supportive care, including:
•evaluation for blood transfusion
•treatment for coinfection
•treatment of seizures

Follow with full course of oral antimalarial:
•ACT
•artesunate plus clindamycin or doxycycline
•quinine plus clindamycin or doxycycline

If illness is with *P. ovale/vivax*, follow with primaquine if not G6PD deficient

Malaria: Prevention

- Bed Nets!!!!!!
  - 1000 nets save 5 lives
    - Insecticide impregnated best
  - Cochrane Review, 2009
- Indoor/personal insecticides
- Vaccine: on the horizon?
  - Some candidates reaching clinical trials, with short-lived efficacy

Take Home Points

- Malaria endemicity and seasonality depends on mosquito habits, seasonality, and *Plasmodium spp*.
- Resistance to medications is species and location dependant
  - If *P. faliciparum*, assume chloroquine resistant
    - Exception: Island of Hispaniola
- Clinical:
  - Who is at highest risk
  - How to differentiate severe vs. uncomplicated malaria
  - Differential diagnosis
- How to choose an anti-malarial treatment:
  - ACTs are preferred therapies, all species
    - ACT if oral, artesunate if IV
  - Severe malaria treated same regardless of species
- Where to find up-to-date resources on Malaria